**Original Investigation**

**Difference in Association of Obesity With Prostate Cancer Risk Between US African American and Non-Hispanic White Men in the Selenium and Vitamin E Cancer Prevention Trial (SELECT)**

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**IMPORTANCE**

African American men have the highest rates of prostate cancer incidence and mortality in the United States. Understanding underlying reasons for this disparity could identify preventive interventions important to African American men.

**OBJECTIVE**

To determine whether the association of obesity with prostate cancer risk differs between African American and non-Hispanic white men and whether obesity modifies the excess risk associated with African American race.

**DESIGN, SETTING, AND PARTICIPANTS**


**MAIN OUTCOMES AND MEASURES**

Total, low-grade (Gleason score < 7), and high-grade (Gleason score ≥ 7) prostate cancer incidence.

**RESULTS**

With a median (interquartile range) follow-up of 5.6 (1.8) years, there were 270,148, and 88 cases of total, low-, and high-grade prostate cancers among African American men and a corresponding 1453, 898, and 441 cases in non-Hispanic white men, respectively. Although not associated with risk among non-Hispanic white men, BMI was positively associated with an increase in risk among African American men (BMI, <25 vs ≥35: hazard ratio [HR], 1.49 [95% CI, 0.95, 2.34]; P for trend = .03). Consequently, the risk associated with African American race increased from 28% (HR, 1.28 [95% CI, 0.91-1.80]) among men with BMI less than 25 to 103% (HR, 2.03 [95% CI, 1.38-2.98]) among African American men with BMI at least 35 (P for trend = .03). Body mass index was inversely associated with low-grade prostate cancer risk within non-Hispanic white men (BMI, <25 vs ≥35: HR, 0.80 [95% CI, 0.58-1.09]; P for trend = .02) but positively associated with risk within African American men (BMI, <25 vs ≥35: HR, 2.22 [95% CI, 1.17-4.21]; P for trend = .05). Body mass index was positively associated with risk of high-grade prostate cancer in both non-Hispanic white men (BMI, <25 vs ≥35: HR, 1.33 [95% CI, 0.90-1.97]; P for trend = .01) and African American men, although the increase may be larger within African American men, albeit the racial interaction was not statistically significant (BMI, <25 vs ≥35: HR, 1.81 [95% CI, 0.79-4.11]; P for trend = .02).

**CONCLUSIONS AND RELEVANCE**

Obesity is more strongly associated with increased prostate cancer risk among African American than non-Hispanic white men and reducing obesity among African American men could reduce the racial disparity in cancer incidence. Additional research is needed to elucidate the mechanisms underlying the differential effects of obesity in African American and non-Hispanic white men.


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African American (AA) men have the highest incidence of prostate cancer of any racial or ethnic group in the United States, and, most importantly, they have the highest rates of aggressive disease and prostate cancer mortality. Elevated risk in AA men may be due to differences in environmental exposures (eg, socioeconomic status and related behaviors) and genetic characteristics, but the specific causes are uncertain. One possibility is that known prostate cancer risk factors differentially affect AA men. Whereas there is no evidence that associations of age, smoking, or family history with prostate cancer differ between AA and non-Hispanic white (NHW) men, it is unknown whether associations of obesity with prostate cancer do. Obesity may be salient to racial disparities in prostate cancer given that it is influenced by environmental and genetic factors, is more prevalent among African Americans, affects physiologic processes associated with cancer etiology, and may affect the sensitivity of prostate-specific antigen (PSA) screening.

The associations of obesity with prostate cancer risk are complex. Studies in primarily NHW populations find that obesity is associated with a decreased risk of nonaggressive (low-grade and/or local stage) disease and an increased risk of aggressive (high-grade and/or advanced stage) disease. Three of 4 case-control studies among black US and Caribbean men, however, found that measures of obesity were associated with increased risks of both low- and high-grade disease. Given the potential importance of this finding, studies that examine the association of obesity with risk among AA men are needed.

The purpose of this study was to compare the associations of obesity with prostate cancer risk between AA and NHW men using data from a large clinical trial that emphasized recruitment of AA men as a study goal.

Methods

Participant and Study Description
Data are from the Selenium and Vitamin E Cancer Prevention Trial (SELECT), a SWOG study conducted in selected academic medical centers and community clinical oncology programs, which tested whether supplementation with selenium, vitamin E, or both would reduce prostate cancer incidence. Between July 2001 and 2004, 35,533 men 55 years or older (≥50 years for AA men) were recruited from 427 study sites in the United States, Canada, and Puerto Rico and enrolled if they had a PSA concentration less than 4 ng/mL (to convert to micrograms per liter, multiply by 1.0) and a normal result on a digital rectal examination (DRE). In total, 4674 AA and 27,566 NHW men participated in the trial. Men were excluded from the present analyses if data were missing on body mass index (BMI, calculated as weight in kilograms divided by height in meters squared) (36 AA and 143 NHW men) or covariates (education, family history of prostate cancer, history of diabetes mellitus, and smoking status; 93 AA and 204 NHW men) or if BMI was less than 18.0 or more than 50.0 (22 AA and 45 NHW men), yielding a sample size of 31,697 (4523 AA and 27,174 NHW men). The primary analyses presented here (conducted in 2014) are based on a sample of 26,071 participants (3398 AA and 22,673 NHW men) who reported PSA and DRE screening within 2 years prior to censoring event.

At a Glance
- African American men have the highest rates of prostate cancer incidence compared with other racial groups in the United States; obesity may play a significant role in these disparities.
- We tested whether associations of obesity and total and grade-specific prostate cancer incidence varied among African American vs non-Hispanic white men.
- Body mass index (BMI) (calculated as weight in kilograms divided by height in meters squared) was inversely associated with low-grade prostate cancer risk within non-Hispanic white men (BMI, <25 vs ≥35: HR, 0.80 [95% CI, 0.58-1.09]; P for trend = .02) but positively associated with risk within African American men (BMI, <25 vs ≥35: HR, 2.22 [95% CI, 1.17-4.21]; P for trend = .05).
- Body mass index was positively associated with risk of high-grade prostate cancer in both populations, although the increase was larger among African American men.
- Reducing obesity among African American men could reduce the racial disparity in prostate cancer incidence.

Event Ascertainment
Cases (n = 1723) were reviewed centrally for pathological confirmation and grading (n = 1575 [91.4%]). Low- and high-grade tumors were defined by Gleason score of 2 to 6 and 7 to 10, respectively. Grade was abstracted from study site pathologic analysis reports for 45 cases and was unknown for 148 cases. Date of death was reported by proxy during study follow-up or was ascertained via Social Security Death Index search if more than 18 months had passed since date of last contact.

Statistical Analysis
Differences in the distributions of demographic and health-related characteristics between AA and NHW men were tested using t test and χ² statistics for continuous and categorical vari-
Table 1. Demographic and Health-Related Characteristics of Screened African American and Non-Hispanic White Men in SELECT

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>African Americans (n = 3398)</th>
<th>Non-Hispanic Whites (n = 22 673)</th>
<th>P Value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean (SD), y</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Education, %</td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>High school or less</td>
<td>31.1</td>
<td>19.1</td>
<td></td>
</tr>
<tr>
<td>Some college</td>
<td>35.7</td>
<td>25.5</td>
<td></td>
</tr>
<tr>
<td>College graduate</td>
<td>19.3</td>
<td>29.2</td>
<td></td>
</tr>
<tr>
<td>Postgraduate</td>
<td>13.9</td>
<td>26.2</td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>17.4</td>
<td>7.8</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Current smoker, %</td>
<td>18.0</td>
<td>5.3</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>BMI, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>18.0 to &lt;25.0</td>
<td>18.8</td>
<td>20.1</td>
<td></td>
</tr>
<tr>
<td>25.0 to &lt;27.5</td>
<td>22.0</td>
<td>27.1</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>27.5 to &lt;30.0</td>
<td>20.3</td>
<td>22.7</td>
<td></td>
</tr>
<tr>
<td>30.0 to &lt;35.0</td>
<td>26.4</td>
<td>22.5</td>
<td></td>
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<tr>
<td>35.0 to 50.0</td>
<td>12.5</td>
<td>7.6</td>
<td></td>
</tr>
<tr>
<td>Family history of prostate cancer, %</td>
<td>18.4</td>
<td>19.9</td>
<td>.04</td>
</tr>
<tr>
<td>Trial arm, %</td>
<td></td>
<td></td>
<td>.41</td>
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<td>Selenium + vitamin E</td>
<td>24.1</td>
<td>25.3</td>
<td></td>
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<tr>
<td>Selenium + placebo</td>
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<td>24.9</td>
<td></td>
</tr>
<tr>
<td>Vitamin E + placebo</td>
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<tr>
<td>Placebo + placebo</td>
<td>26.2</td>
<td>25.2</td>
<td></td>
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</tbody>
</table>

Abbreviation: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared).

* P values by test for continuous variables; P values by χ² test for categorical variables.

were adjusted for age, education, history of diabetes, current smoking, family history of prostate cancer, and study treatment arm. To test whether associations of obesity with cancer risk differ between AA and NHW men, models included multiplicative interaction terms of race and BMI. Statistical analyses were performed using Stata SE software, version 12.0 (Stata Corporation). All statistical tests were 2 sided, and P < .05 was considered statistically significant.

Sensitivity Analyses

We performed 5 sets of sensitivity analyses to evaluate the robustness of our primary analyses, which are detailed in the eMethods in the Supplement. Briefly, we (1) repeated analyses after randomly assigning grade, (2) modeled death as a competing risk, (3) allowed for race-specific effects of diabetes on risk, (4) repeated analyses after censoring at date of study protocol nonadherence, and (5) repeated analyses using all AA and NHW men regardless of screening status.

Results

During a median (interquartile range) of 5.6 (1.8) years of follow-up, 1723 men developed prostate cancer. Table 1 and Table 2 give demographic and health-related characteristics of AA and NHW SELECT participants included in this study. In general, AA men were a mean of 4.2 years younger (due in part to study eligibility criteria), had lower educational attainment (33.2% vs 55.4% completed college; P < .001), and had a higher prevalence of diabetes, smoking, and obesity (38.9% vs 30.1% had BMI ≥ 30; P < .001). The incidences of total, low- and high-grade, and locally staged prostate cancer were significantly higher among AA men. The overall covariate-adjusted effects of AA race were HR of 1.58 (95% CI, 1.37-1.81; P < .001), 1.34 (95% CI, 1.12-1.61; P = .002), and 1.81 (95% CI, 1.42-2.30; P < .001) for total, low-grade, and high-grade cancers, respectively.

Table 3 gives the associations of BMI with total cancer for AA and NHW men using NHW men with BMI less than 25 as the referent group. Looking across table rows shows the relationship between obesity and prostate cancer risk within race groups with the P value testing for linear trend. Looking down table columns shows the effect of race within BMI groups, which we present as the AA race effect with the P value testing for interaction. Obesity was not associated with risk of total prostate cancer among NHW men. Among AA men, however, there was a significant positive association between obesity and total prostate cancer risk. Looking within AA men only, the HR contrasting BMI less than 25 to BMI at least 35 was 1.49 (95% CI, 0.95-2.34; P for trend = .03) and the corresponding AR was 157.3 (95% CI, 94.1-275.3) cases per 100 000 person-years. The AA race effect increased across BMI categories and ranged from 28% (61.8 cases per 100 000 person-years) among those with BMI less than 25 to 103% (219.1 cases per 100 000 person-years) among those with BMI at least 35 (P for trend = .03). Results were similar when cases were restricted to those with known grade, with the exception of AA men with BMI less than 25. More than 30% of these men had ungraded...
cancer, compared with 9.5% among AA men with higher BMI (P < .001). As a result, their incidence of graded cancer was substantially lower, which attenuated the AA race effect among men with BMI less than 25.

Associations between BMI and grade-specific prostate cancer are given in Table 4 using NHW men with BMI less than 25 as the referent group. For low-grade cancer, obesity was inversely associated with prostate cancer risk among NHW men but positively associated with risk among AA men. Within NHW men, those with BMI at least 35 had a 20% reduced risk (~61.0 cases per 100,000 person-years) compared with those with BMI less than 25 (P for trend = .02). Looking within AA men only,
the HR contrasting BMI less than 25 to BMI at least 35 was 2.22 (95% CI, 1.17-4.21; P for trend = .05) and the corresponding AR was 287.7 (95% CI, 98.6-831.9) cases per 100,000 person-years. The AA race effect on low-grade cancer increased significantly with increasing BMI, ranging from a nonsignificant 20% reduced risk (−61.3 cases per 100 000 person-years) among men with BMI less than 25 to a 122% increased risk (287.3 cases per 100 000 person-years) among men with BMI at least 35 (P for trend = .005). For high-grade cancer, the association of obesity with risk was substantially larger among AA than NHW men. Within NHW men, those with BMI at least 35 had a 33% increased risk (6.2 cases per 100 000 person-years) compared with those with BMI less than 25 (P for trend = .01). Within AA men, the HR contrasting BMI less than 25 to BMI at least 35 was 1.81 (95% CI, 0.79-4.11; P for trend = .02) and the corresponding AR was 19.4 (95% CI, 4.2-89.1) cases per 100,000 person-years. Unlike the finding for low-grade cancer, the AA race effect did not differ significantly across obesity categories (P for trend = .41).

Findings from sensitivity analyses are given in eTables 1 through 5 in the Supplement. Notably, when ungraded cancers were assigned a grade on the basis of the distribution of low- and high-grade disease, the excess risk for cancer among AA compared with NHW men with BMI less than 25 increased from −20% to +12% for low-grade cancer and from 32% to 41% for high-grade cancer. However, the findings contrasting the associations of obesity with risk in AA compared with NHW men were unchanged.

### Discussion

In this large prospective study, we found substantial differences in the associations of obesity with prostate cancer risk among AA compared with NHW men. In analyses of total prostate cancer, obesity was positively associated with risk among AA men only. In grade-stratified analyses, obesity was inversely associated with the risk of low-grade cancer and positively associated with the risk of high-grade prostate cancer among NHW men but positively associated with risks of both low- and high-grade prostate cancer among AA men. As a consequence, the AA race effects for total and low-grade prostate cancer were substantially larger than among NHW men.
cancers were substantially higher among men with BMI at least 25 compared with men with BMI less than 25. In contrast, the AA race effect for high-grade cancer differed little across BMI categories.

Evaluating associations on the additive scale is important to ascertain the actual number of prostate cancer cases attributed to obesity, and this information is lacking for AA men. Using the observed covariate-adjusted rates (per 100,000 person-years) of 234.1, 298.4, and 18.6 for total, low-grade, and high-grade cancer in NHW men in SELECT with BMI less than 25 as the reference group, we can calculate the excess risk or attributable risk percent (ARP) for any contrasts in our tables. From a clinical perspective, we found that among AA men in SELECT, having a BMI at least 30 vs a BMI less than 25 was associated with 141.2 additional cases of total prostate cancer per 100,000 person-years, which is an ARP of 28.6%. The ARP associated with obesity for total prostate cancer among NHW men in SELECT is close to zero, which is consistent with studies finding no association unless cancer is stratified by grade.14,15 The estimated ARP for obesity and any cancer among primarily NHW men in the United States is 4%,25 and to our knowledge, our study is the first to report these for grade-specific prostate cancer, albeit within the context of a clinical cohort. Here the ARPs due to obesity among AA men are 47.4% and 46.1% for low- and high-grade disease, respectively, which is substantially higher than the modest negative and 20.4% ARP for low- and high-grade cancer among NHW men.

Our finding of an overall 58% increased risk for prostate cancer among AA compared with NHW men is consistent with other studies.26 Our findings on obesity and prostate cancer risk among NHW men are also similar to those of many recent studies that have found that associations between obesity and prostate cancer risk differ by cancer aggressiveness.14,15,27 In a meta-analysis of 12 prospective studies, Discacciati and colleagues14 found an inverse association between BMI and localized prostate cancer (RR, 0.94 [95% CI, 0.91-0.97]; P for trend < .001) and a positive association between BMI and advanced prostate cancer (RR, 1.09 [95% CI, 1.02-1.16]; P for trend < .001). Similar findings were reported in the Prostate Cancer Prevention Trial15 and REDUCE (Reduction by Dutasteride of Prostate Cancer Events)27 studies, which used prostate biopsy to confirm presence or absence of cancer.

We know of only 1 study that has examined whether associations of obesity with prostate cancer risk differ between AA and NHW men. This case-control study found a nonsignificant inverse association of obesity with total and advanced prostate cancer risk among AA men but a positive association among whites.19 Three small case-control studies have reported associations between central adiposity and prostate cancer risk among AA men that are consistent with the findings reported here.16,18,28 Findings from all of these studies, however, are not reliable because of the many inherent biases in case-control studies, which influence both the strength and direction of associations.29 More prospective studies are needed to confirm the findings given here.

The mechanisms underlying our findings are unknown. One possible explanation is that the biological effects of obesity differ in AA and NHW men. Inflammation plays a role in prostate carcinogenesis,30 and the effect of obesity on systemic inflammation could be stronger in AA than in NHW men.31 Similarly, insulin may play a role in prostate carcinogenesis32 and it is possible that the effect of obesity on insulin secretion is stronger in AA than in NHW men. There is consistent evidence that both fasting and postprandial insulin levels are higher in AA than in NHW men,33 but we know of no studies that have examined whether obesity increases these differences. There are also known prostate cancer risk alleles (eg, CYP3A4 single-nucleotide polymorphism, 8q24 region phB2 single-nucleotide polymorphisms, and androgen receptor CAG repeat polymorphism) that are more prevalent among AA men34,35 with which obesity may interact and modify their function.37

Another possible explanation is that detection of prostate cancer, despite screening recommendations based on site-based standard of care, may still be higher among AA compared with NHW men in SELECT. Mean PSA concentrations, adjusted for age and other covariates, are lower among NHW compared with AA men,36-38 which may increase the likelihood that AA men receive diagnostic biopsies. Furthermore, it is well established that obesity is inversely associated with PSA concentration,36-41 although the mean difference in PSA, contrasting men with BMI at least 35 to those with BMI less than 25, is small (roughly 0.2 μg/mL). It is possible, however, that the associations of obesity with PSA differ between NHW and AA men. Whereas Fowke and colleagues36 found no difference in the association of obesity with PSA in AA and NHW men, Culp and colleagues38 reported that the odds of having a PSA level at least 4.0 ng/mL, contrasting BMI less than 25 to at least 30, decreased by 6% (P < .02) in NHW men but increased by 113% (P = .11) in AA men. If, indeed, obesity is associated with an increase in PSA level among AA men, we believe it likely that PSA level is functioning as an indicator of disease risk and not a cause of detection bias.

The strengths of this study include its large sample size, standardized assessment of height and weight, active follow-up for incident prostate cancer, and consideration of bias due to differential detection. Specifically, our primary analysis included only men who were screened in the 2 years prior to their censoring event. We also performed several sensitivity analyses (given in eTables 1, 3, and 5 in the Supplement) addressing racial differences in the percentage of ungraded cases, the risk of death, the prevalence of diabetes, and adherence to study protocol, which reinforced the stability of our primary findings. There are also several limitations. Body mass index is a nonspecific measure of obesity because it does not distinguish more metabolically active abdominal fat from other body fat42 and it does not distinguish whether excess body weight relative to height is attributable to fat or nonfat tissues.43 However, in the Prostate Cancer Prevention Trial, associations of obesity with prostate cancer risk were stronger for BMI than any measure of central adiposity.15 Even in our relatively large sample of AA men, the number of cases within categories defined by both grade and BMI were small. Although findings in the screened sample were similar to those in the full cohort, there may still be possible racial differences in the proportion of men who elected to undergo biopsy following...
an elevated PSA test result. Finally, these results may not generalize to the population at large given the fact that men from SELECT comprise a clinic-based sample.

Conclusions

Findings from this study suggest that increased obesity could partially explain the substantially higher risk of prostate cancer among AA men. Not only is obesity more strongly associated with increased prostate cancer risk among AA men, it is considerably more prevalent among this group. This study reinforces the importance of obesity prevention and treatment among AA men, for whom the health benefits may be comparatively large. Although obesity is linked to poor health outcomes in all populations, clinicians might consider the unique contribution of obesity prevention and treatment to the health of their AA patients. Such targeted efforts may contribute to reductions in prostate cancer disparities.

REFERENCES

Editor’s Note

Targeted Reduction in Body Mass Index Is a Worthwhile Risk Reduction Strategy for Prostate Cancer

Charlie R. Thomas Jr, MD

Although it is well known that African American men have a higher incidence and mortality from prostate cancer, the reasons behind this epidemiological phenomenon are not clearly defined. If risk factors for the development of prostate cancer can be identified, it is possible that primary care practitioners may be able to focus on risk reduction strategies. To this end, the study by Barrington et al1 in this issue of JAMA Oncology presents results via joint-effects modeling to describe the effect of an interaction between race and obesity on risk of prostate cancer. Barrington et al1 have identified differential body mass index (BMI; calculated as weight in kilograms divided by height in meters squared) as contributing to the increased incidence of this disease in a cohort of African American men enrolled in the SELECT (Selenium and Vitamin E Cancer Prevention Trial). There appears to be a 4 times greater risk of developing prostate cancer in African American men as the BMI increases (28% for BMI < 25 vs 103% for BMI ≥ 35). Furthermore, the risk of developing high-grade disease (defined as a Gleason score ≥ 7) was associated with higher BMI in all patients, although this risk was higher in African American men compared with non-Hispanic white men (hazard ratio, 1.81). Despite the limitations inherent in the methodology utilized for the analysis and the inability to define a clear mechanism behind the association between BMI and risk, the findings do provide a further rationale for weight reduction and a target BMI for clinicians to aim for in care of African American men.

Conflict of Interest Disclosures: None reported.